Purdue Pharma
Shareholders & Board Meeting

Thursday, July 22, 2010
10:00am
Board Room

Questions Arising During the Presentations

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1. Compliance

1.1 Does the fact that some representatives appear to have promoted Ryzolt for the treatment of mild pain signify a "failure" in sales training? Also, given our past experience with promotion of OxyContin, is the training of our representatives broad, deep and significant enough on new products?

While there may have been some level of confusion with the analgesic "step training" (i.e. WHO ladder of treatments for mild, moderate and severe pain) considering the absolute number of sales calls and the very low incidence of reference to "mild" or "milder" pain, legal/compliance believe the sales training was both adequate and appropriate. In a broader sense, we are faced with ongoing and significant changes in pharma regulations, both at the state and federal level, and ensuring adherence to and compliance with these changing demands is under close and constant scrutiny.

1.2 Is the cost of tracking our expenditures on meals and other expenditures on healthcare providers exceeding the costs themselves?

No, the tracking costs are actually quite modest. Moreover, even if we decided to eliminate all such expenditures, we would still need the tracking systems – to meet the data reporting and quality system requirements of some of the legislation.

1.3 There is a lack of clarity about reporting requirements for personal contributions/expenditures by Directors. Specific and clear guidance is required for both political contributions and interactions, as well as for meal and entertainment expenses by Directors – for both Purdue and ex-Purdue purposes.

As the Board members will recall, a recent memo on Lobbying Disclosure requirements was disseminated to the Board. If there are follow-up questions

regarding the issues covered in the memo or on other aspects of Lobbying Disclosure obligations, they should be directed to Robin Abrams. Redacted

Redacted

2. Butrans

2.1 A question over changes in flux rate over the course of the seven day dosage interval was answered by Brian Burke. No follow up action required.

2.2 Would sales be improved if Butrans was sampled directly to physicians?

There isn't a clear answer, since some MD's state a preference for physical samples whereas others state a preference for pharmacy-based sampling approaches. The plan is to proceed with a pharmacy-based approach (i.e. sample card) but we will consider whether or not to also establish a physical sampling program.

Action: RG

2.3 Provide the Board with the market research on pricing & rebating and further details of the proposed pricing (e.g. how the price compares to key competitive products, etc.). In addition, show month by month sales forecast, decompose by strengths, show price and units as well by strength, show kg of Buprenorphine by strength, and put the unit sale onto the international chart on a per capita basis for all of the companies.

The response to this question will be provided in a separate communication directly from the Marketing department.

Action: RG

2.4 Provide a comparison of sales projections of Butrans to the actual sales performance of all significant analgesic product launches over the past 10 years – including but not limited to Embeda, NuCynta, Ultram, Ultram ER, Opana ER, Lyrica and Flector.

The response to this question will be provided in a separate communication directly from the Marketing department

Action: RG

2.5 Provide the Board with more information on the strategy/tactics with respect to KOL's, how they are identified, how do we plan to interact with them, how do we see them helping build appropriate utilization of Butrans - and any other relevant information that will/could influence the prescribing of the product.

A detailed overview of the KOL Product Information Programs for Butrans is being developed for future presentation to the Board.

Action: RG

2.6 There were general questions about the effects of various sorts of external heat sources on flux rate and pharmacokinetics, and especially how this may be of particular concern in Japan.

The FDA approved labeling for Butrans includes the following statement: "Advise patients and their caregivers to avoid exposing the Butrans application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system because an increase in absorption of buprenorphine may occur. Advise patients against exposure of the Butrans application site and surrounding area to hot water or prolonged exposure to direct sunlight. There is a potential for temperature-dependent increases in buprenorphine released from the system resulting in possible overdose and death."

This statement is of particular interest in Japan where hot water baths are commonplace.

Below is summarized the events surrounding the statements in the FDA approved US Full Prescribing Information (FPI) regarding heat exposure. There was no FDA correspondence specifically on this isolated issue; however, the details below provide the regulatory background on this topic.

In September 2009, Purdue's version of the FPI, submitted with the Complete Response in September 2009, contained brief statements in the Warnings and Precautions section related to patients with fever and application of external heat. These warnings were based on the findings from our clinical pharmacology studies BP96-1102 (Endotoxin Challenge) and BP98-1204 (External Heat), which were further described in the Clinical Pharmacology section of the proposed FPI at that time. We also proposed brief statements in the Information for Patients and in the Medication Guide related to this issue.

In April 2010, Purdue received FDA's revisions to the FPI. Among their changes, FDA added a boxed warning that included text about avoiding exposure of the patch to heat, including the statement "Temperature-dependent increases in buprenorphine released from the system may result in possible overdose and death." FDA also revised all of the additional sections where this issue is discussed (Warnings, Clin Pharm, etc) with similar wording.

It appears FDA has imposed this wording based on the data submitted in our NDA and their experience with the fentanyl transdermal patch (e.g. Duragesic). The wording proposed by FDA for the Butrans FPI was nearly identical to that in the Duragesic label (attached). Overdose, including severe respiratory depression and death, have been associated with Duragesic, including reports which have suggested that exposure of the patch to direct heat may increase risk by increasing plasma fentanyl levels. FDA has issued two public health safety alerts related to the risk of overdose with Duragesic (July 2005 and again December 2007 including a Dear Health Care Provider letter), which have included warnings about the risks of exposing the Duragesic patch to external heat sources. The FDAs warning about Duragesic can be found at:

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152289.htm

While no deaths have been reported in association with Butrans exposed to external heat, in our study BP98-1204, we demonstrated that plasma levels of buprenorphine increase when the Butrans patch is exposed to external heat. This was accompanied by an increase in the reported incidence of adverse events. Given that application of heat increased buprenorphine delivered from the patch, FDA is concerned and does not want to see a repeat of the Duragesic experience.

We counter-proposed wording to FDA in response to their proposals for all of these sections of the FPI. FDA did substantially reduce the statements in the boxed warning as we had proposed, however, the statements about the possible serious outcomes remains

Action: CL/JHS

2.7 Why is there no reference to efficacy data in the marketing materials?

Sales and Marketing are currently working closely with Clinical, Legal and Regulatory to determine what specific efficacy statements can be made – given the products approved labeling and supporting clinical trial data. The discussion of efficacy is included in the selling materials; however a specific reference or statement to Butrans providing efficacy for 7 days seems to be the desired statement. Due to the design and data collection schedules in the Phase III clinical study program, we may not have data that supports efficacy at that specific time point. There are sections of the promotional materials that discuss the results of the two pivotal trials that demonstrated efficacy versus placebo, which were the basis for FDA approval.

Action: RG/CL/PS/LDS

2.8 The reference to "oral" in the statement "does what no oral analgesic can…" was not seen as very impactful – since it is obvious to a healthcare provider that oral medicines need to be taken regularly. What was the "runner up" positioning statement, and how did it score relative to the current statement?

The runner up was statement BO: Butrans - the 7-day transdermal matrix delivery system can be the baseline treatment for opioid-naïve patients, providing them with around-the-clock pain treatment.

On the measure of Overall Impression of Product P Based on Positioning Statements (% Rating 8, 9, or 10 on 10-pt scale*), statement BO scored a 7.2 versus the winning statement CA of 7.5.

Among some groups, statements other than CA perform well on select metrics. However, none of these perform universally as well as statement CA. In fact, CA performed well within every subgroup, winning every group, even as other statements performed well on select metrics. In total, statement BO is a strong performer as it gains 2nd ranking for motivation, overall impression, and communicating important info.

Action: RG/CL

2.9 What can be said in response to a prescriber who asks directly or indirectly…"can this product be prescribed for my patient with OA?" In responding are we required to specifically mention the failed trials in OA, and is there an adequate mechanism for describing or managing the conversations concerning the failed trials?

Sales and Marketing are currently working closely with Clinical, Legal and Regulatory – as part of a larger project to develop a list of Frequently Asked Questions (FAQ's) and approved responses. Questions for the FAQ document are being generated from both U.S. markets research projects and actual sales representative experience in Australia, Canada and the U.K. In general however, the indication is not limited to any one pain condition. While not yet formally approved by MRL, a response to "can this product be prescribed for my patient with OA?" should begin with the indication, "Doctor, Butrans is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time and is not limited to any particular condition. It is up to your clinical judgment as to whether or not Butrans is an appropriate therapy for any particular patient." The label for Butrans also includes the statement: "One study in osteoarthritis, that included an active comparator, failed to show efficacy for Butrans and the active comparator." The study referred to in the labeling was a randomized, active-control, parallel group study with a 3-month double-blind phase to evaluate the efficacy and safety of BTDS 20 and OxyIR relative to BTDS 5 in subjects with moderate-to-severe osteoarthritic pain of the hip or knee (Study BUP3019). The study population included subjects who were 40 years of age or older, had Grade II to IV OA of the hip or knee, and were adequately treated with their stable opioid analgesic regimen of 30 to 80 mg/day of oral morphine or its equivalent for at least 4 days a week in the 30 days prior to entry. There were no statistically significant differences observed between either BTDS or OxyIR and BTDS 5 in the primary efficacy analysis. The study did not demonstrate assay sensitivity (subjects did not respond to gold standard pain medication OxyIR) and therefore has met the statistical/clinical definition of a "failed" study.

The current draft response about clinical trial efficacy includes the following:

One additional 12-week low back pain study involving Butrans did not reach statistical significance for the treatment difference in average pain scores at the Week 12 time point as did in the other 2 low back pain studies. This study had a small sample size and was not powered to statistically compare the treatment group difference at this time-point - which could be a reason the study did not meet this efficacy endpoint. Because Butrans did not meet the efficacy endpoint of the study, this is a negative trial.

The 4th study was an osteoarthritis pain study. It was a failed trial in which neither immediate-release oxycodone 40 mg/day, a known effective pain regimen, nor Butrans 20 mcg/hour provided a statistically significant difference from the control, Butrans 5 mcg/hour, in average pain scores. Therefore, because the active control (oxycodone 40 mg/day) did not provide a statistically significant improvement, no conclusion can be drawn regarding the analgesic effect of Butrans from this study.

Action: RG/CL/PS/LDS

2.10 Consider developing a chart showing US, EU, Canada, and Australian labeling - so that overlapping and differing aspects may be noted.

In process, but because of the very different ways that labeling information is presented in the various countries, and the fact that some countries have labeling that addresses certain issues that others don't – this will be practical to do for only a limited number of key considerations such as indications, contraindications, warnings, etc.

Action: RG

2.11 Is there anything of value in the HECON data submitted to the Scottish Medicines Consortium?

The Butrans submission to the SMC is a complex document containing many analyses. Among other things, it demonstrates that Butrans can be seen as being more cost-effective than some other Step 3 opioids (oxycodone and fentanyl) in patients who have not responded to Step 2 opioids (codeine preparations and tramadol). In that sense, it is helpful. However, since it is based upon pricing, treatment protocols and clinical studies that are different from those in the U.S., it is not directly applicable in the U.S.

2.12 Do we track IMS scripts for region "O"? What is the rate of "no call" MD's and if rising, what is the driver? Do we also have no call or no sell pharmacies?

Yes, IMS still tracks scripts for Region "0" prescribers. The attached file shows scripts, dollars and units for no-call prescribers that have written a script for our products in the last 24 months. As a reminder, some no-call prescribers do not write for our products so they will not be listed in the file. There is also a Summary tab that shows totals for all OER scripts for prescribers in Region 0 - which shows trending for the last two years.

The rate of no-call prescribers assigned to Region 0 is rising and it's hard to determine the exact drivers. Some possibilities are:

- increased rep training on RSOP 1.7.1
- increase in prescriber visibility due to new data sets
- new websites for looking up DEA license status
- Google and other web alerts

- increase in the actual number of reps in the field in the last few years
- increase in the # of prescribers researched by the Law Department
- increase in data auditing by Home Office

The chart shows the number of no-call prescribers we have assigned to Region 0 since 2001. The data behind this chart is also included in the file.

Region 0 June 2010.xls

We also have no call pharmacies, although only began that practice with the creation of our Order Monitoring System ("OMS") in 2009. So there are many fewer pharmacies in that designation than prescribers. Since we do not sell directly to retail pharmacies, we do not have a category of "no sell" pharmacies.

Action: RA/RG

2.13 Since Butrans is a divertible, abusable compound, what are the specific programs/plans to address this – so as to not have a repeat of the abuse problem that emerged with OxyContin?

Analyses of buprenorphine according to the 8 factors of the Controlled Substances Act indicate that buprenorphine is an opioid with a potential for abuse that is lower than that of prototypic Schedule II morphine-like opioids (i.e. pure mu agonists). This conclusion is based on the convergence of a broad range of data including affinity for the mu-opioid receptor, its partial agonist and mixed agonist-antagonist pharmacology, human and animal abuse potential, and studies of its physical dependence and withdrawal producing properties.

The transdermal buprenrophine formulation (Butrans) is not predicted to increase the abuse potential of buprenorphine because it further limits the onset of buprenorphine's effects compared to sublingual or parenteral formulations. Furthermore, high dosage sublingual formulations are presently widely available to opioid-dependent persons because they are indicated and marketed for use by this population.

It is possible to extract the buprenorphine from BTDS patches, but this appears unlikely given the ready access to other more readily abusable forms of buprenorphine and to other opioids with higher intrinsic abuse potential. Furthermore, buprenorphine extraction from transdermal systems has not been evidenced in Europe where such formulations have been available for several years.

The foregoing conclusions are not intended to imply that buprenorphine is without abuse or physical dependence potential. In fact, nonclinical and clinical data support the conclusion that buprenorphine has significant abuse potential, and that its abuse potential is lower than that of morphine-like opioids. Similarly, physical dependence and withdrawal appear generally weaker following chronic buprenorphine administration than chronic administration of morphine-like opioids. Consistent with these conclusions, human abuse potential and clinical trial data indicate that the Butrans formulation has lower abuse potential relative to other buprenorphine formulations or opioid products.

Although tampering and extraction are possible, the pharmacology of buprenorphine, the ready availability and low cost of morphine-like opioids would make tampering relatively unattractive given the investments of time and effort required. The partial opioid agonist pharmacology of buprenorphine also has public health and safety implications. In particular, buprenorphine has ceiling effects on respiratory depression and euphoria, thus reducing the risk of overdose death relatively to morphine-like opioids.

Despite Butrans having a potentially lower abuse potential relative to other opioids, we plan to be extremely diligent not to have a repeat of the abuse problem that emerged with OxyContin.

In collaboration with FDA, we have developed a Risk Evaluation and Mitigation Strategy (REMS) to educate healthcare professionals about potential risks associated with Butrans. The goals of the REMS are to inform patients and healthcare professionals about the safe use of Butrans including potential for abuse, misuse, overdose, and addiction. The plan includes providing educational materials, conducting ongoing and frequent assessments, and implementing targeted interventions as needed. Key educational elements of the plan include:

- *Healthcare Provider Training Guide:* A training guide has been developed specifically for prescribers concisely describing potential risks of abuse, misuse, overdose, and addiction from exposure to Butrans along with providing information on appropriate patient selection, dosing and administration, and safe use of the product.

- *Dear Doctor Letter: A letter* designed to convey and reinforce risks associated with Butrans and emphasize the REMS program goal has been developed for distribution to dispensers and other healthcare professionals.

- *Medication Guide:* A medication guide has been developed specifically for patients to warn them of the risks along with providing information on safe use, proper storage, and appropriate disposal methods for Butrans. We are ensuring that this guide is available for distribution to patients receiving prescriptions for

Butrans by providing sufficient numbers to distributors and authorized dispensers.

This FDA-approved educational information will be mailed to over 75,000 healthcare providers, and made available to all healthcare professionals via our corporate REMS website (www.Butransrems.com). Field Sales force and Medical Services Department distribution is also planned.

Assessment of the REMS educational program will be accomplished by evaluating abuse and overdose related information (related to Butrans and/or other opioids) using data from a variety of national and proprietary databases including: the Researched Abuse Diversion and Addiction Related Surveillance System (RADARS); the FDA Adverse Event Reporting System (AERS); the National Survey on Drug Use and Health (NSDUH); the Monitoring the Future Study (MTF); the Drug Abuse Warning Network (DAWN); and, the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO). In addition, post-marketing and epidemiologic study development is being evaluated.

Action: CL

2.14 A question was raised concerning disposal and the effect on the environment with "fold-and-flush"

The FDA-approved full prescribing information label for Butrans currently states "When changing the system, remove Butrans, fold it over on itself, and flush it down the toilet. Alternatively, Butrans can be sealed in the Patch-Disposal Unit provided and then disposed of in the trash."

The Butrans NDA included submission of the results of an environmental exposure assessment study (PKDM/ Toxicology Department Report). The study was conducted for Butrans in accordance with guidelines of the *Committee for Medicinal Products for Human Use, Guidance on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/ CHMP/ SWP/4447/00, June 2006). Based on the results of this assessment, it was concluded that the prescribed usage of buprenorphine base by patients is unlikely to pose a risk for the environment.

The Butrans NDA also included a specific study assessing the effect of a disposed BTDS on septic system performance. Based on the results of this assessment, it was recommended that Butrans *not* be disposed in a residence with a septic system given that the patch contains layers which are not readily biodegradable; however, occasional disposal of a Butrans into a septic tank is not expected to significantly affect septic tank function. Therefore, the Butrans Patch-Disposal Unit was developed as alternative to fold-and-flush method.

WJM 8-12-10